Chronic exposure to fibrin and fibrinogen differentially regulates intracellular Ca2+ in human pulmonary arterial smooth muscle and endothelial cells.

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Public Summary:

Scientific Abstract:
Acute pulmonary embolism occurs in more than half a million people a year in the United States. Chronic thromboembolic pulmonary hypertension (CTEPH) develops in approximately 4% of these patients due to unresolved thromboemboli. CTEPH is thus a relatively common, progressive, and potentially fatal disease. One currently proposed theory for the poor resolution advocates that modification of fibrinogen in CTEPH patients causes resistance of emboli to fibrinolysis. The current study investigated the regulation of cytosolic Ca(2+) ([Ca(2+)](cyt)), central to the control of cell migration, proliferation, and contraction, by chronic exposure of pulmonary artery smooth muscle (PASMC) and endothelial (PAEC) cells to fibrinogen and fibrin. Basal [Ca(2+)](cyt) was substantially elevated in PAEC after culture on fibrinogen, fibrin, and thrombin and in PASMC on fibrinogen and fibrin. In PAEC, fibrinogen significantly decreased the peak [Ca(2+)](cyt) transient (P <0.001) without a change in the transient peak width (at 50% of the peak height). This response was independent of effects on the proteinase-activated receptor (PAR) 1. Furthermore, chronic exposure to thrombin, an activator of PAR, significantly reduced the peak agonist-induced Ca(2+) release in PAEC, but increased it in PASMC. The recovery rate of the agonist-induced [Ca(2+)](cyt) transients decelerated in PASMC chronically exposed to fibrin; a small increase of the peak Ca(2+) was also observed. Substantial augmentation of PASMC (but not PAEC) proliferation was observed in response to chronic fibrin exposure. In conclusion, chronic exposure to fibrinogen, fibrin, and thrombin caused differential changes in [Ca(2+)](cyt) in PAEC and PASMC. Such changes in [Ca(2+)](cyt) may contribute to vascular changes in patients who have CTEPH where the pulmonary vasculature is persistently exposed to thromboemboli.